Concluding remarks Day 1

The Evolution of Biopharmaceutics: Risk Assessment and Clinical Relevance

Helena Engman, PhD
Senior Principal Scientist, ADME Sciences

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Day 1. Essence and Reflections\

Session 1. Laid out the important foundation

Biopharmaceutics Risk Assessment

- Integrating dissolution data with in vivo understanding supports patient-centric quality and regulations

Framework – FDA and Industry working group (IQ/AAM)

- Assessing the risk of not achieving the desired in vivo performance following oral administration
- IR and MR in same
- Risk level dictates the evidence required
- Science-driven, using quantitative, continuous measures
- Integrates use of predictive tools and totality of evidence (in vitro, preclinical, clinical)

Principles

- Informed, proactive risk decisions
- Mitigation strategies proportional to risk level
- Increasing understanding may enable risk reduction (downgrading)

Benefits

- Aligned terminology
- Facilitated decision-making (industry and regulatory)
- More efficient development with reduced timelines and cost

Session 2 & 3.
High & Medium Risk categories
→ This is where the framework will make the most difference

Session 2. High risk category \

- Products where rate and extent of drug absorption are dictated by in vivo drug release.

- Core characteristics
  - All ER formulations; IR products with complex solubilization technologies (amorphous solid dispersions, lipid-based, nanoparticles); formulation technology controls in vivo PK.

- Strategies for mitigation including potential downgrading & role of dissolution:
  - In vivo PK studies with 3–4 formulations; Level A IVIVC preferred for BCS Class 1 ER; IVIVR or PBBM-based safe space where Level A not feasible; advanced biorelevant methods.
  - *Virtual BE?*
  - *Predictive dissolution modelling?*

Session 3. Medium risk category \

- Core characteristics:
  - BCS Class 2 drugs where GI physiological conditions (pH variability, bile salts, food) meaningfully affect dissolution and absorption; permeability is favorable.
- Strategies for mitigation including potential downgrading / role of of dissolution:
  - Biorelevant dissolution methods (FaSSIF/FeSSIF); discriminating ability against key attributes; PBBM strongly encouraged. 1-2 clinical studies for validation.

  - *Advanced in vitro technology eg TNO TIM-1.*
  - *IVIVR/Safe space*
  - *Dissolution technology and PBBM goes hand in hand to investigate mechanisms behind absorption limitations, predict absorption and develop methods for justification of clinical relevance*

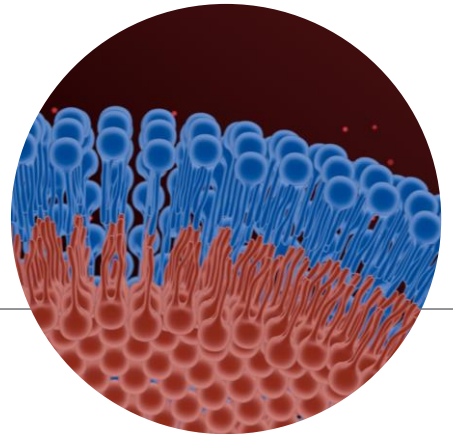
Permeability in its Context - Biopharmaceutics Risk Assessment \

- Oral absorption – a complex, multi-step process – need to balance focus on dissolution
  - Assign permeability a clear role in BRA
  - Not (well) captured by dissolution testing
- Shift to continuous measures
  - Strong, formulation-independent PK exist despite moderate or low permeability.
  - Permeability cut off limits need to be revisited and revised for higher resolution
- Intrinsic (passive) permeability (Fredlund et al., 2017) is used in the BRA framework used in AstraZeneca (Engman et al., 2025).

- Correlation established between intrinsic permeability and human fraction absorbed (Fabs)
- Permeability is defined as Low when corresponding to Fabs <20%

Permeability classification*	Human Fabs
High	≥85%
Moderate	20-84%
Low	<20%

* Fredlund et al., 2017



Fredlund L. et al. In Vitro Intrinsic Permeability: A Transporter-Independent Measure of Caco-2 Cell Permeability in Drug Design and Development. Mol. Pharmaceutics 2017, 14, 1601−1609. https://doi.org/10.1021/acs.molpharmaceut.6b01059

Engman H. et al. Leveraging Biopharmaceutics Bridging Risk Assessment and In Vivo Predictive Tools to Accelerate Immediate Release Drug Product Development by Minimized Need for Clinical Bridging Studies. Mol. Pharmaceutics, 2025, 22, 6203−6214. https://doi.org/10.1021/acs.molpharmaceut.5c00910

Extended Release (ER) profile – Colon absorption \

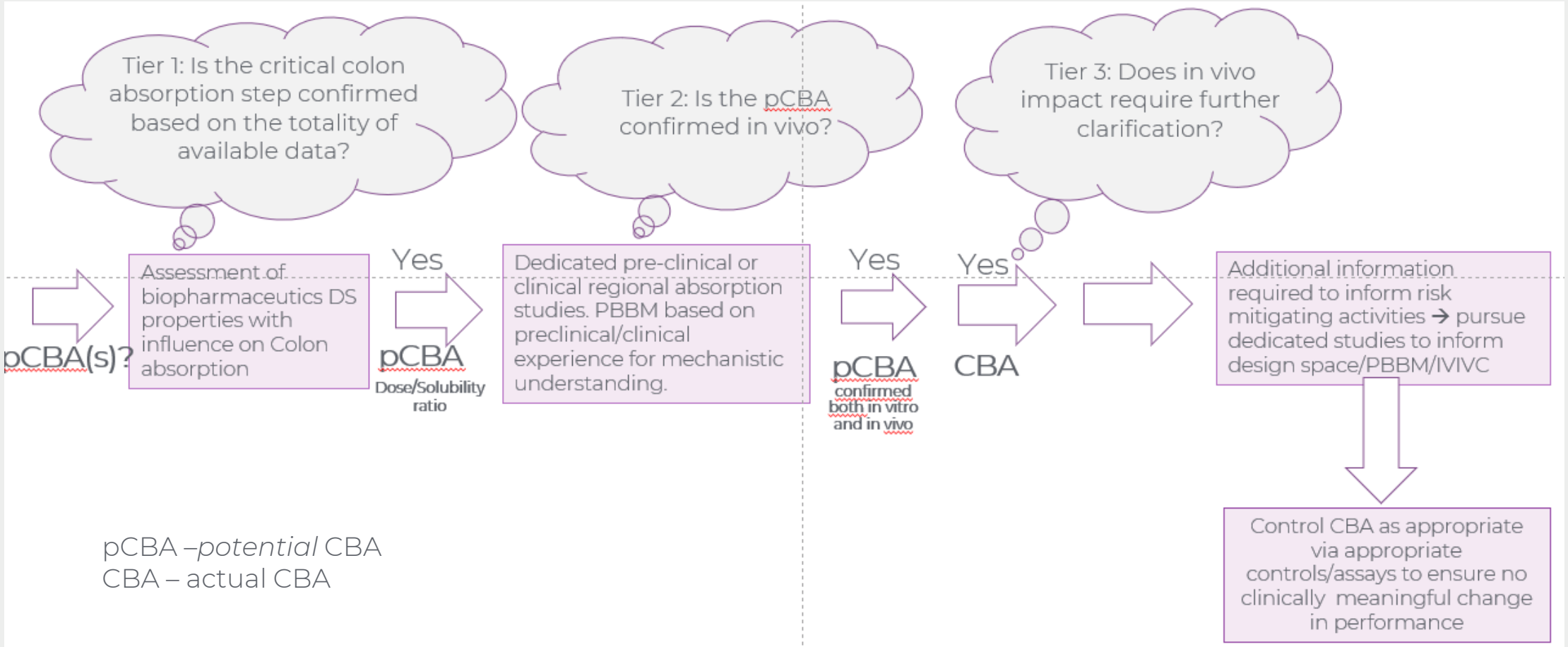
- ER products with release profiles >3-5 hours release a portion of the dose in the colon
  - Need to ascertain a certain degree of colon absorption
- Specific conditions in colon makes absorption more challenging
  - Permeability: tighter epithelium, much smaller surface area
  - Stability under microbial and anaerobic conditions
  - Solubility: Low volume of free fluid
    - Dose:Solubility Ratio – critical for release/dissolution
- Colon absorption is a significant component of Biopharm Risk Assessment (predicts success/failure rate for ER product development)
- Clarify/diversify regarding complexity depending on release profile

Builds \

1. Assign permeability a clear role in Biopharmaceutics Risk Assessment, BRA
2. Revise principles for interpretation of permeability
    - From categorical to continuous
    - Revised cut off limits
3. BRA and CBA identification for Extended release (ER) products
    - Two parallel biopharmaceutics workflows - drug substance and product for release profiles >3-5 hours
        - Drug substance: Investigate potential for colon absorption
        - Product: Target release profile and colon absorption weighed together for successful development

Identifying and Understanding the Absorption Limiting Factor(s) – Drug Substance \

HIGH/VERY HIGH risk – Extended Release



pCBA –*potential* CBA
CBA – actual CBA

Thank you

Looking forward to continuing discussions tomorrow!

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